CNS Neuroscience & Therapeutics

REVIEW

CNS Neuroscience & Therapeutics

Vagomimetic Effects of Fingolimod: Physiology and Clinical Implications

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Keywords
Atrioventricular block; Bradycardia; Cardiac electrophysiology; Fingolimod.

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Received 17 December 2013; revision 17 April 2014; accepted 20 April 2014

doi: 10.1111/cns.12283

SUMMARY

Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator approved to treat relapsing-remitting multiple sclerosis (MS). Initiation of treatment with fingolimod has been found to produce transient bradycardia and/or slowing of atrioventricular impulse conduction in a small proportion of patients. This effect is thought to be due to the interaction of fingolimod with S1P receptors on the surface membrane of atrial myocytes causing a vagomimetic effect, similar to the action of acetylcholine on muscarinic receptors. As a precaution, patients are under electrocardiogram (ECG) monitoring for 6 h after receiving their first dose. Fingolimod is contraindicated in patients with overt or concealed cardiac diseases. However, the Fingolimod Initiation and caRdiac Safety Trial (FIRST), which was designed specifically to investigate the cardiac profile of fingolimod, did not show an increased risk of clinically relevant cardiac events with fingolimod. This review examines the electrophysiology and pathophysiology of cardiac impulse formation in the context of fingolimod. It concludes that these vagomimetic effects should be considered benign and should not prevent the effective use of fingolimod in the treatment of patients with MS.

Introduction

Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator approved for the treatment of relapsing-remitting multiple sclerosis (MS) [1]. Treatment initiation has been found to produce a generally asymptomatic, dose-dependent, transient bradycardia, and/or slowing of atrioventricular (AV) impulse conduction in a small proportion of patients [2–4]. Phase II and III clinical study data from over 3500 patients show no evidence of an increased risk of serious cardiovascular events versus placebo or standard of care [5]. Nevertheless, patients receiving fingolimod must be monitored for 6 h after treatment initiation for signs and symptoms of bradycardia [6,7]. In addition, fingolimod is currently contraindicated in patients with overt or concealed cardiac diseases, which may range from defects in impulse generation and conduction to ischemic heart disease and failure [6,7]. This review will explore the mechanistic rationale for these effects and examine the cardiac safety data available to date from clinical studies. To better understand the clinical relevance of these effects, the electrophysiology and pathophysiology of cardiac impulse formation will be explained.

Fingolimod and Vagomimetic Effects: Mechanism and Clinical Findings

Fingolimod is an S1P receptor modulator [1]. S1P receptors are predominantly expressed by lymphocytes, neural cells, and cardiac tissue cells [1,8–10]. MS is an autoimmune disorder of the central nervous system (CNS), and fingolimod is thought to exert its therapeutic effects via S1P receptors on lymphocytes ($S1P_1$, $S1P_4$) and neural cells ($S1P_1$, $S1P_3$, $S1P_5$) [1]. It is thought that fingolimod also binds to $S1P_1$ receptors on the surface membrane of atrial myocytes, leading to a short-term, $S1P_1$-Gαi-dependent activation of the G-protein-gated potassium channel, IK_{ACh}, before internalization and/or desensitization of the receptors [1,11]. The direct consequence of this binding is a vagomimetic effect, similar to the action of acetylcholine on muscarinic receptors, causing an initial heart rate (HR) reduction (maximal reduction in mean HR = 8 bpm) as well as prolongation of AV impulse conduction in some patients [2–4,11,12]. This reduction in HR is generally asymptomatic, becomes visible within a few hours after the first dose, peaks within 6 h, and then gradually returns to normal [2–4].

The transitory effects of fingolimod 0.5 or 1.25 mg once daily were investigated in three pivotal Phase III studies (FREEDOMS, FREEDOMS II, and TRANSFORMS). Hourly HR was taken for the first 6 h postdose, electrocardiogram (ECG) was recorded 1 day before the first dose and at 6 h postdose, and 24-h Holter ECG monitoring was conducted after dosing in FREEDOMS II [3]. Of the 1212 patients treated with fingolimod 0.5 mg, only one had HR ≤ 40 bpm after dosing. Clinical symptoms of bradycardia following treatment initiation were reported in 0.8% of patients treated with fingolimod 0.5 mg. The rate of second-degree AV blocks was low, and most occurred during the first 6 h after dosing. Furthermore, there were no cases of Mobitz Type II or higher AV blocks (Table 1) [3].

To further characterize these cardiac effects, the Fingolimod Initiation and caRdiac Safety Trial (FIRST) was designed to assess any first-dose-related cardiac events with fingolimod 0.5 mg once daily in a relapsing-remitting MS patient population [13]. The FIRST study included patients with cardiac risk factors excluded from Phase III studies. These cardiac risk factors included recurrent symptomatic bradycardia, resting HR at baseline of 45–54 bpm, a history of positive tilt test, concomitant treatment with beta-blockers and other HR-lowering drugs, and a history or presence of Mobitz Type I second-degree AV block. Ambulatory ECG monitoring was conducted for 24 h at screening and for at least 6 h after administration of the first dose of fingolimod.

Of the 2415 patients who received at least one dose of fingolimod, 2282 patients completed the study, including 295 patients who had preexisting conditions/baseline cardiac findings (12.2%; Table 2) [13].

Overall, first-dose monitoring in the FIRST study did not reveal an increased risk of clinically notable cardiac events with fingolimod. The incidence of AV blocks on ECGs was low, irrespective of the presence of cardiac risk factors. The AV blocks were benign, Mobitz Type I second-degree AV blocks, with no cases of Mobitz Type II or complete AV blocks. Moreover, the results were deemed similar to those observed in previous controlled fingolimod trials, where cardiac effects of treatment initiation were generally benign [2–4]. The frequency of cardiac adverse events within 48 h of treatment initiation in the FIRST study was only slightly higher in patients with preexisting cardiac conditions (2.4%) compared with the rest of the patient population (2.0%) [13]. There were six serious adverse events reported in five patients within 4 months after treatment initiation that were classified as cardiac disorders (angina pectoris, second-degree AV blocks, bradycardia, cardiac disorder, cardiovascular disorder, and sinus bradycardia) [13]. None of these patients were in the cardiac risk group or were receiving beta-blockers or other HR-lowering drugs. All events manifested within 48 h of receiving the first dose except for one that occurred 41 days postdose (reported as cardiovascular disorder with moderate symptoms of dizziness, hypotension, and nausea).

The transient and benign nature of the first-dose effects of fingolimod has been further confirmed in the Evaluate Patient OutComes (EPOC) study [14]. In 783 patients transitioning from a standard-of-care disease-modifying therapy to fingolimod, the nadir HR was reached by 5 h postdose (mean change from baseline, −8.3 bpm) and began to recover by 6 h. The rate of symptomatic bradycardia was low (1%), with spontaneous recovery in all cases. Furthermore, of the 139 patients who had a postdose ECG, there were no cases of advanced AV block.

Table 1 Pooled cardiac and Holter ECG findings from three fingolimod Phase III studies (TRANSFORMS, FREEDOMS, and FREEDOMS II) [3]

Event	Fingolimod 0.5 mg (n = 1212)	Fingolimod 1.25 mg (n = 1219)
Nadir mean HR reduction from baseline	−8.1 bpm	−11.4 bpm
Mean HR ≤ 40 bpm for any 1 h, 0–6 h postdose, n (%)	1 (0.3)	5 (1.4)
Symptomatic bradycardia (%)	0.6	2.1
Wenckebach (Mobitz Type I) second-degree AV blocks (%)*		
0–24 h postfirst dose	3.7	6.7
<6 h postfirst dose	2.6	5.0
6–24 h postfirst dose	1.1	1.7
2:1 second-degree AV blocks (%)*		
0–24 h postfirst dose	2.0	3.3
<6 h postfirst dose	1.4	2.5
6–24 h postfirst dose	0.6	0.8
Day 1 Mobitz Type II or higher AV blocks	0.0	0.0

AV, atrioventricular; bpm, beats per minute; ECG, electrocardiogram; HR, heart rate. *Data from FREEDOMS II only (n = 1212 and n = 1219 for 0.5 mg and 1.25 mg, respectively).

Table 2 Incidence of AV blocks on ambulatory ECG recording: 6 h pretreatment versus following administration of first dose of fingolimod 0.5 mg by subgroups and by type of AV block in relapsing patients with MS (FIRST; safety set) [13]

Number of patients with events* (%)	No PCCs (n = 2120)	PCCs (n = 295)	BBs/CCBs (n = 120)
Pretreatment ambulatory ECG			
Mobitz Type I second-degree AV block	0	12 (4.1)	0
2:1 AV block	0	2 (0.7)	0
Postdose ambulatory ECG			
Mobitz Type I second-degree AV block	18 (0.9)	12 (4.1)	0
2:1 AV block	7 (0.3)	6 (2.0)	0
Patients with events both predose and postdose	0	6 (2.0)	0
Patients with new postdose events	19 (0.9)	6 (2.0)	0

AV, atrioventricular; BB, beta-blocker; CCB, calcium channel blocker; ECG, electrocardiogram; FIRST, Fingolimod Initiation and caRdiac Safety Trial; MS, multiple sclerosis; PCC, preexisting cardiac conditions or baseline cardiac findings. Reprinted from Gold R et al. *J Neurology* 2013. Published under the Creative Commons License 2.0 CC-BY. *Some individuals had two types of second-degree AV block (Mobitz Type I and 2:1 AV block).

Electrophysiology and Pathophysiology of Cardiac Impulse Formation and Conduction

Bradycardia, defined by convention as a resting HR of less than 60 bpm, is a common, often transient, feature of both healthy and diseased individuals [15,16]. In most cases, even severe bradycardia can be asymptomatic, and usually, there are no short- or long-term consequences [15,16]. Bradycardia most frequently reflects high cardiac vagal activity, and it can be observed in trained athletes and healthy young adults while resting or sleeping [17–23]. In general, bradycardia only becomes problematic in certain people with concomitant diseases affecting the cardiac conduction system [15,16].

The cardiac conduction system comprises the sinus node, the atrioventricular node, the His bundle, the right and left bundle branch, and the Purkinje system, with a hierarchy where the sinus node is the primary pacemaker of the heart [24].

Sinus Node Dysfunction

Sinus node dysfunction (SND) is also referred to as sick sinus syndrome. This syndrome includes a variety of disturbances affecting impulse formation and transmission in the sinus node. SND is typically a disease of the elderly and tends to be both chronic and progressive. The incidence of SND doubles between the ages of 50–60 years and 60–70 years, with a peak incidence at 70–90 years [15,25]. The prevalence of SND is approximately 1 in 600 patients over the age of 65 years. There is no definitive information about the exact incidence of the disease, but it is estimated to be in the range of 150–200 patients per million [26].

Sinus node dysfunction may be due to either intrinsic pathological processes in the sinus node or extrinsic causes [27]. The most frequent cause of SND is thought to be an intrinsic degenerative process secondary to the senescence of the sinus node and surrounding tissue. This process results in the progressive death of pacemaker cells and a shift in the location of the impulse formation within the sinus node [28,29]. Among the extrinsic factors, the use of cardiovascular drugs (calcium channel blockers, β-adrenergic blockers, digoxin, and antiarrhythmic agents) is the most frequent cause of SND. However, these drugs do not necessarily lead to conventional SND, but to forms of asymptomatic bradycardia that a patient can easily tolerate. There are also several noncardiovascular drugs whose side effects include bradycardia and conduction disturbances (Table 3).

There is a marked variation in resting HR among healthy, asymptomatic individuals. The "normal" range of HR during the day is 46–93 bpm in men and 51–95 bpm in women [30]. HR decreases during sleep by an average of 24 bpm in young adults and 14 bpm in the elderly over 80 years of age. One series of 24-h ambulatory ECGs in healthy, asymptomatic individuals of all ages showed that marked and transient HR decreases are common during sleep. These included HR of 30–35 bpm, sinus pauses of 1.5–2.5 seconds, sino-atrial blocks, junctional rhythms, and first- and second-degree AV nodal blocks [17–21]. Indeed, these findings are common enough to be considered normal variants. Furthermore, highly trained athletes are prone to bradycardia, with HRs below 40 bpm common at rest [22,23]. In a study by Viitasalo et al. [22], sinus pauses of 2–3 seconds were found in 37% of athletes during sleep.

Table 3 Drugs used in clinical practice that have bradycardia and/or conduction disturbances listed as possible side effects

Drugs with non-CV indications	Drugs with CV indications
Benzodiazepines	Alpha-adrenergic agonists (phenylpropanolamine)
Clonidine*	Class Ib AA (lidocaine, mexiletine, phenytoin*)
Lithium	Class Ic AA (flecainide, propafenone)
Ophthalmic beta-blockers (timolol)	Class II AA beta-blockers
Opiates	Class III AA (amiodarone, sotalol, dofetilide, bretylium)
Phenytoin*	Class IV AA (diltiazem, verapamil) and other calcium antagonists
Physostigmine, neostigmine	Digitalis glycosides
Propoxyphene	Dronedarone
Sultopride	Ticagrelor
Tricyclic antidepressants	

AA, antiarrhythmic; CV, cardiovascular. *Both CV and non-CV indications.

Consequently, it is not possible to precisely define a HR threshold differentiating between SND and a normal, albeit severe, bradycardia. In addition, some cases of severe bradycardia may have a specific, reversible cause. For example, patients with obstructive sleep apnea and hypoxia may show episodes of severe bradycardia that can be eliminated with appropriate treatment [31,32].

Atrioventricular Conduction Block

The ECG presentation of SND is highly variable, ranging from classical sinus bradycardia to arrest of the sinus node activity. This leads to a failure of an expected atrial activation due to a defect in sinus node impulse generation or a failure of impulse conduction to the atrium, respectively [33]. AV conduction block is a rhythm disorder in which atrial impulses are conducted with a delay or not conducted to the ventricles at all during a period when the AV conduction pathway is not expected to be refractory. The incidence of acquired AV conduction defects increases with age and can be as high as 30% [34,35]. AV blocks are the major reason for pacemaker implantation [36].

Based on ECG criteria, AV blocks are classified as first, second, or third degree [37]. First-degree AV block is defined as PR interval prolongation above 200 ms, that is, every atrial impulse is conducted to the ventricle with a constantly prolonged PR interval. Second-degree AV block is defined as intermittent failure of AV conduction and is classified as either Type I (Mobitz I or Wenckebach) or Type II (Mobitz II). Type I second-degree AV block is characterized by progressive prolongation of the PR interval until the atrial impulse is not conducted to the ventricle (i.e., the P wave is not followed by a QRS complex), and it is usually seen in conjunction with a narrow QRS. The resumption of conduction shows a shorter PR interval after the blocked beat. Type II second-degree AV block appears as a fixed PR interval before and after a

blocked beat, and it is usually associated with a wide QRS complex. A 2:1 AV block occurs when every other P wave is blocked (also known as "advanced AV block"). A 2:1 AV block cannot be classified as Type I or II second-degree AV block based on a single (short) recording of the surface ECG. The presence of an intraventricular block indicates a block distal to the AV node, whereas a block with a small QRS complex is usually within the AV node. Third-degree AV block (complete heart block) is defined as absence of AV conduction, leading to complete dissociation between the atrial and the ventricular rates, with the former being higher than the latter.

Similar to SND, acquired AV block can be caused by several extrinsic and intrinsic factors. Also, systemic diseases (amyloidosis, sarcoidosis [38]), neuromuscular disorders (muscular dystrophy, Kearns-Sayre syndrome), and neoplastic disorders (primary cardiac lymphoma [39], postradiation therapy [40]) may be associated with AV conduction disturbances. They can also occur as a consequence of radiofrequency ablation of accessory pathways for AV nodal re-entrant tachycardia [41,42]. Idiopathic progressive degeneration of the cardiac conduction system, known as "Lenegre" [43] or "Lev" [44] disease, may be involved in almost 50% of all cases of AV block. AV block can occasionally be induced by exercise, and, if not due to myocardial ischemia, it is often due to a diseased His-Purkinje system. In this instance, the prognosis is poor unless a pacemaker is implanted [45].

The prognosis of patients with AV conduction disturbances also depends on the underlying heart disease. First-degree AV blocks are associated with an excellent prognosis as the risk of progression to third-degree AV block is extremely low [46–48]. Typically, they are completely asymptomatic and only noticed if the patient has an ECG for other medical reasons. In healthy young individuals or in well-trained athletes with normal QRS width, Type I AV block is a benign condition [49]. In patients over 45 years of age or in patients with associated bundle branch block, the prognosis is worse compared with age- and sex-matched individuals, and a pacemaker is usually implanted [50,51]. In general, older patients with asymptomatic Type I second-degree AV block should be monitored closely, and a pacemaker fitted if they become symptomatic. Type II second-degree AV block carries a high probability of progression to a complete AV block, and a pacemaker implant is expected to significantly improve the 5-year survival rate [50,52]. In Type II second- and third-degree AV block, the implantation of a pacemaker is mandatory, even in the absence of symptoms.

Evaluation and Management of SND and AV Blocks

In each patient, it is vital to analyze the degree of correlation between signs or symptoms and ECG findings. In SND, there is a wide range of symptoms, including heart failure symptoms, CNS symptoms such as mental incapacity, near syncope or syncope, dizziness, light headedness, vertigo, nonspecific symptoms (fatigue, lethargy), and specific cardiovascular symptoms (angina, dyspnea). In addition, more subtle symptoms might be observed, such as digestive disturbances, periodic oliguria or edema, and modest effort intolerance. In the case of AV block, patients presenting with advanced block generally complain of dizziness, vertigo, and/or syncope, but may also suffer from the same symptoms as those seen with SND, or may be completely asymptomatic [27,53–56].

Consequently, it is important to carefully assess the patient from a clinical point of view as well as from the instrumental point of view. For SND and AV blocks, the clinician has various tools to correlate symptoms with bradycardia. The standard 12-lead ECG is the primary one. However, there are other useful tools, both invasive and noninvasive. Ambulatory ECG monitoring (over 24 or 48 h) is the most straightforward and is helpful in patients presenting with frequent symptoms [57,58]. Patients with random symptoms are most suited to assessment using external or implantable loop recorders [59]. The support of an electrophysiologist is indicated when diagnosis is uncertain or when pacemaker implantation is clearly indicated.

The European Society of Cardiology (ESC) and European Heart Rhythm Association (EHRA) guidelines for cardiac pacing [16] indicate that no intervention is needed in patients with episodes of asymptomatic sinus bradycardia (with HR as low as 30 bpm), sinus pauses of up to 3 seconds, first-degree AV block, or Type I second-degree AV block. Indeed, these findings should all be considered to be within the normal range. Consequently, the first step for extreme asymptomatic bradycardia should be to rule out any extrinsic causes of SND and to exclude a physiological sinus bradycardia. Any reversible causes of AV block (electrolyte abnormalities, acute myocardial ischemia or infarction, drugs that can be discontinued, inflammation, sleep apnea, or vagotonia) should be corrected/treated.

It is important to note that treatment is not necessarily required for asymptomatic SND (including SND caused by essential use of bradycardia-inducing medication), asymptomatic first-degree AV block, or asymptomatic second-degree Type I with supra-Hisian conduction block.

Vagal Activation in the Ischemic and Failing Heart

The vagomimetic action of Fingolimod has triggered concerns about its safety. Such a concern was reiterated in consecutive FDA reports. The agency though caused for caution was using Fingolimod in specific cardiac disorders as those discussed here above. However, in the cardiology community, pharmacologic and nonpharmacologic vagal activation is sought for as the novel approach to ischemic heart disease and heart failure. Representative of this concept is a leading study linking vagal activity and cardiac risk, where Cole et al. [60] noted that, "A delayed decrease in the HR during the first minute after graded exercise, which may be a reflection of decreased vagal activity, is a powerful predictor of increased cardiac risk, independent of workload, the presence or absence of myocardial perfusion defects, and changes in HR during exercise". Indeed, a large volume of experimental and clinical data support the role of the sympathetic nervous system in the initiation of lethal cardiac arrhythmias [61,62]. Vagal activation is then appreciated as the most physiological tool to inhibit excessive sympathetic activation.

In view of the concerns generated by the vagal-like activity of fingolimod, we will briefly describe hereafter how not only

short-lasting vagal interventions, but also chronic ones are safe and beneficial in patients with overt cardiac disease.

Almost two decades ago, experimental evidence documented the protective effects of vagal activity against lethal cardiac events [63]. The individual autonomic profile, where either vagal or sympathetic tone can dominate, was studied by looking at beat-to-beat variation in HR and vagal reflex bradycardia during increases in blood pressure. The clinical consequence of this experimental observation was the multicenter, international trial, Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI). ATRAMI prospectively showed that baroreflex sensitivity and HR variability are both strong and independent predictors of cardiac mortality. Specifically, preserved vagal control of cardiac activity after myocardial infarction was associated with longer, event-free survival [64].

This evidence has generated a growing interest in interventions that are able to modulate the sympatho-vagal control of HR. The underlying concept that high cardiac vagal activity may be beneficial in the ischemic heart is supported by evidence in animal models, where augmentation of vagal activity appears to protect against lethal ischemic arrhythmias [63,65,66]. The use of vagal nerve stimulation (VNS) has recently been exploited in the heart failure arena, where morbidity and mortality are the greatest challenge to contemporary cardiology. In the preclinical setting, in dogs with heart failure caused by high-rate ventricular pacing, 12-week VNS was associated with significantly lower left-ventricle (LV) end-diastolic and end-systolic volumes and higher LV ejection fraction (LVEF) compared with untreated animals [67]. Furthermore, in a chronic ischemic experimental model of heart failure, VNS at a low intensity (without causing HR reduction) exerted a positive effect on LV function and heart failure biomarkers [68]. An analysis of 32 New York Heart Associate Class II–IV patients showed a nonsignificant reduction in LV end-diastolic volume, a significant reduction in LV end-systolic volume, and a significant increase in LVEF after VNS stimulation [69].

Clinical Applications of Chronic Vagal Nerve Stimulation

Vagal nerve stimulation is used in the clinical setting to treat drug-refractory epilepsy [70,71] and, more recently, depression [72]. The stimulation protocol for such applications of VNS is designed to prevent HR changes. Notably, among the several thousand patients chronically stimulated to date, no safety issues on AV conduction have been raised as this therapy received FDA approval.

A recent clinical study investigated the potential benefit of VNS in heart failure [69]. This study assessed the safety and tolerability of chronic VNS in patients with symptomatic chronic heart failure (CHF) and severe LV systolic dysfunction, using a newly designed implantable nerve stimulation device. A secondary aim was the preliminary assessment of clinical efficacy. The main finding from this study was that chronic VNS in patients with advanced systolic CHF was well tolerated and may improve quality of life and LV function. In the context of this review, an important safety aspect of chronic VNS in patients with cardiac disease is that there have been no new reports of AV conduction abnormalities in the presence of an expected mild, but significant, HR reduction. Although the number of patients in this study was small, the vagal effect exposure was chronic.

Serious Adverse Events

Examining the experimental and clinical evidence and current guidelines suggests that the transient vagomimetic effects of fingolimod are, in most cases, benign and not unusual in otherwise healthy subjects with high vagal tone. Exercise training chronically increases cardiac vagal activity and, by this mechanism, has been associated with increased health benefits and reduced cardiovascular mortality [73,74]. In the context of this review, a patient with vagotonia who experienced symptomatic long-lasting bradycardia after treatment with fingolimod [75] and a patient treated with risperidone who developed asystole and sustained bradycardia after receiving the first dose of fingolimod deserve consideration [76]. Specifically, in the first case, a sustained bradycardia was observed in a 30-year-old man. At nadir, 9 h after fingolimod first intake, HR was 33 b/min and symptomatic for dizziness. The symptoms resolved with atropine and HR returned to control values within 4 days. In the second case, a 20-year-old man in multiple therapy including risperidone suffered a sinus pause 7.5 seconds long. Following this pause, malaise and convulsive movements were observed. Symptoms resolved spontaneously, and patient felt rapidly "OK". In this case, a potentiation of the vagomimetic action of fingolimod by risperidone is the most logical mechanism. As matter of fact, asystole episode longer than 7.5 seconds is not infrequent in young people undergoing tilt testing and is not perceived as life threatening in young people. A wrong perception of the autonomic mechanisms in lethal tachy arrhythmias has led some authors to link these two cases to sudden arrhythmic death, an event described in advanced MS. It must be clearly understood that, specifically in young people, sudden death occurs because of ventricular fibrillation triggered by sympathetic hyperactivity while vagal activation is a physiological protective mechanism with strong antiarrhythmic effects [61]. Thus, the vagomimetic action of fingolimod cannot be advocated, by any means, as linked to sudden arrhythmic death.

Globally, as of August 2013, there has been 101,000 patient-years of exposure to fingolimod, and treatment initiation information from the postmarketing safety database is consistent with clinical trial data. The frequency of symptomatic bradyarrhythmias has remained low at 0.17 per 100 patient-years during the previous 6 months safety reporting period. Similar to the results from the clinical studies, the majority of these events occurred on day 1 and were transient (Data on File, Novartis Pharma AG, 2013).

Conclusions

Fingolimod causes a transient HR reduction immediately following treatment initiation. Although few cases of symptomatic bradycardia and second-degree AV block have been reported, 6-h cardiac monitoring is recommended and fingolimod is contraindicated in patients with certain cardiac conditions. Overall, we believe that the vagomimetic activity of fingolimod should not prevent its effective use in the treatment of patients with MS. Furthermore, a better understanding of the HR effects of $S1P_1$ modulation may even lead to new drug candidates in the cardiovascular arena.

Acknowledgments

Editorial support for this manuscript was provided by Richard Knight, PhD, of Complete Medical Communications and was funded by Novartis Pharma AG.

Conflict of Interest

This manuscript has not been published or submitted elsewhere. The authors declare no conflict of interest.

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